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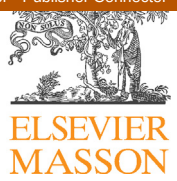

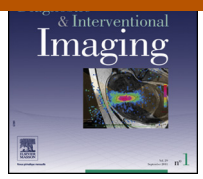

REVIEW / *Musculoskeletal imaging*

Role of ultrasound in assessing remission in rheumatoid arthritis

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KEYWORDS
Rheumatoid arthritis;
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Abstract
Introduction: Remission is the ultimate goal of the treatment of rheumatoid arthritis (RA). However, the diagnosis of remission might still be vague. Musculoskeletal ultrasound (US) seems to effectively assess synovitis, effusion and bone damage. Thus, its role could be relevant for the diagnosis, monitoring or detection of relapse in the follow-up of RA in remission. The goal of this review of the literature was to clarify the added value of ultrasonography during remission.
Methods: A systemic search of the literature was performed on Medline and Scopus. The following key words were used: rheumatoid arthritis, remission, US. Fifty-six papers were collected, then after an in depth analysis, twelve articles were selected for analysis.
Results: Twelve papers were identified that assessed remission in RA. Remission criteria varied from one author to another. The number of joints assessed by US varied from six to 44 with the wrist and metacarpo-phalangeal joints of the dominant hand scanned at least. Irrespective of remission criteria, all authors demonstrated that US detected Doppler positive synovitis in patients in clinical remission. Also, power Doppler synovitis predicted structural damage and future flares of RA.
Conclusion: US seems to be more effective than a clinical exam. True remission in RA must be defined. Moreover, the inclusion of this technique in the new definition of remission is being validated.
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Abbreviations: ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; DP, Power Doppler Ultrasound; PGA, Patient Global Assessment; GPA, Global Physician Assessment; EULAR, European League Against Rheumatism; SH, Synovial Hypertrophy; PIP, Proximal Interphalangeal Joints; MCP, Metacarpo-Phalangeal Joints; MTP, Metatarso-Phalangeal Joints; TJC, Tender Joint Count; SJC, Swollen Joint Count; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; OR, Odds Ratio; RA, Rheumatoid Arthritis; SDAI, Simple Disease Activity Index.

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Introduction

In the past few decades, the rate of remission in rheumatoid arthritis (RA) had increased thanks to the intensive prescription of disease modifying antirheumatic drugs [1] and the introduction of biotherapies when necessary [2]. A specific strategy of treating early RA adapted to each patient and including close follow-up, called ''Treat To Target'' is now being implemented [3]. Indeed, it has been shown that soon after the onset of RA, there is a period of time called a window of opportunity when effective treatment can induce remission in a significant number of patients [4]. Obtaining remission in RA is our ultimate goal because this is the only way to prevent structural progression and articular damage. Several definitions of remission have been established and all of them take into account clinical and biological criteria. However, numerous studies have shown evidence of persistent infra-clinical synovitis on imaging, in particular with musculoskeletal ultrasound (US) [5—7]. Moreover, musculoskeletal US has now been proposed as one of the remission criteria for monitoring RA [8].

The goal of this review of the literature was to assess the role of US in evaluating RA in remission, to determine which joints should be assessed, and which scores should be used.

Materials and methods

We performed a systematic search of the literature from 2005 to 2013 using the Medline and Scopus databases with the following keywords: rheumatoid arthritis; remission and ultrasound. Fifty-six papers were identified. Only articles published in French or English were selected. Seven articles were excluded because they evaluated US on vessels and three others MRI. Thirteen articles evaluated active RA. Clinical cases; letters; and editorials were also excluded. A total of twelve articles that met our criteria were selected for analysis.

A summary of the selected articles is provided in Fig. 1.

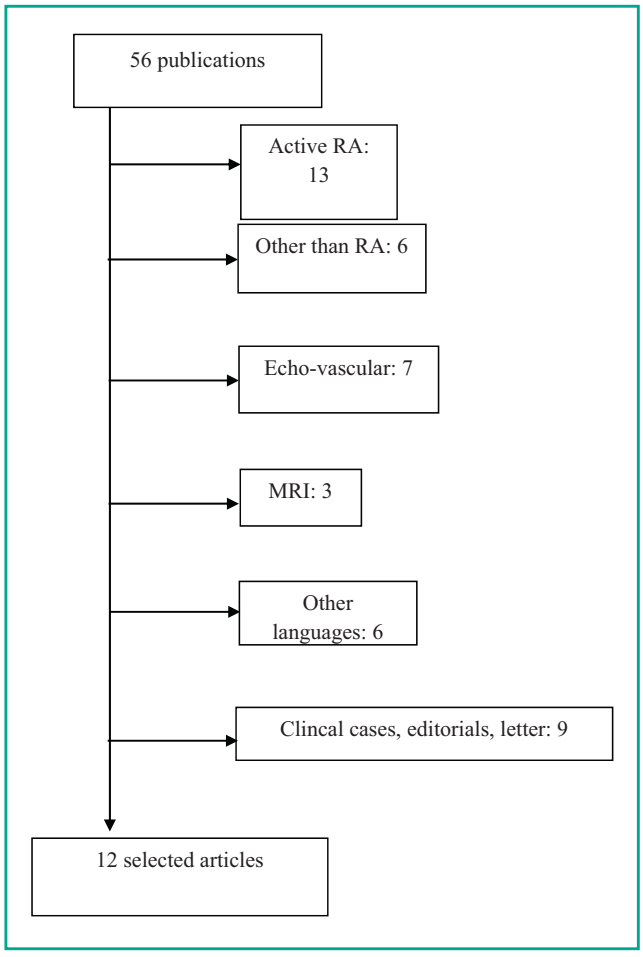

Figure 1. Selection of articles.

Results

Our review of the literature included 12 articles evaluating the role of osteoarticular US in patients followed-up for RA in remission. All studies were prospective. The main results are summarized in Table 1.

First, we looked at the definitions of « remission » that were used in different studies. We then identified the different joints and scores used in US. Finally, the added value of US for monitoring remission was identified in each study.

Definition of remission

Inclusion criteria varied from one study to another. In 4/12 articles, remission was based on the physician's judgment [9—12]. However, objective composite scores to evaluate RA activity showed that numerous patients were not in remission. The different scores used included the modified American College of Rheumatology (ACR) criteria, the Disease Activity Score of 28 joints (DAS 28), and/or the Simple Disease Activity Index (SDAI) (Appendix 1). The percentage of patients in remission according to these different scores is summarized in Table 2. When ACR or DAS 28 criteria were used, between 76 and 54% of patients were in remission. When SDAI criteria were used (with a cutoff of 3.3), only 29 to 44% were in remission. The duration of remission according to these scores varied from 2 [13] to 6 months [14—17].

Ultrasound assessment, number of joints tested and scoring

The physicians assessing joints on US were blinded to clinical and biological findings in all the articles in this study. All operators used B-mode to assess synovial hypertrophy (SH) and Power Doppler (PD) to assess synovial vascularization. The OMERACT 2005 (Outcome Measures in Rheumatoid Arthritis Clinical Trials) [18] definitions were used to define B-mode and PD synovitis.

Joint scores

B-mode SH and PD hypervascularization were determined using a semi-quantitative score in all studies except one. When a semi-quantitative score was used, a grade of 0 to 3 was assigned to each joint depending on the extent of B-mode SH and then these scores were added together. Also, a score of 0 to 3 was used for each joint depending on the extent of DP synovial vascularization and the scores were

Table 1 The added value of ultrasonography RA remission according to different studies.

Author Year	Population	Remission criteria	Joints scanned	US findings: B-mode synovitis	US findings: PD synovitis	Clinically healthy joints (number, %)	PD infra-clinical synovites (number, %)
Brown et al., 2006 [9]	107 RA remission	Physicians' judgment Period > 6 months	8 wrist (4 sites) MCP 2-5 of the dominant hand	84.9%	60.4%	725. 86%	241. 33%
Wakefield et al., 2007 [20]	10 early RA	DAS28 < 2.6 Period > 6 months	42 shoulders, elbows, wrists, MCP, PIP, knees, ankles, MTP	For patients in remission: 50.7%	For patients in remission: 15.2%	Not specified	Not specified
Brown et al., 2008 [10]	102 RA remission	Physicians' judgment	8 wrist (4 joints) MCP 2-5 Dominant hand	84%	51%	378. 82%	56. 15%
Saleem et al., 2009 [14]	100 RA Remission	DAS28 $\leq$ 2.6 Period > 6 months	6 wrist 5 MCP Dominant hand	87%	46%	450. 75%	227. 50.5%
Sciré et al., 2009 [19]	106 RA 43 remission	DAS $\leq$ 1.6 Period > 3 months	44 shoulders, sterno et acromio-clavicular joints, elbows, wrists, MCP, PIP, knees, ankles, MTP	For patients in remission: 95%	For patients in remission: 41%	Not specified	Not specified

RA: rheumatoid arthritis; DAS: Disease Activity Score; MCP: metacarpo-phalangeal; IPP: proximal interphalangeal; MTP: metatarso-phalangeal.

Table 2 Percentage of patients in remission according to the different RA activity scores in the articles with physicians' judgment as a remission criterion.

Authors reference	Remission according to physicians' judgment (number)	ACR (%)		DAS28 < 2.6 (%)		SDAI < 3.3 (%)	
		Remission	Active	Remission	Active	Remission	Active
Brown et al., [9]	107	55	45	57	43	–	–
Brown et al., [10]	102	–	–	56	44	–	–
Balsa et al., [11]	97	75	25	76	24	44	56
Naredo et al., [12]	76	–	–	54	46	29	71

Table 3 Scoring of B-mode synovitis.

Grade 0 or Normal	Normal joint: no synovial thickness, no joint effusion
Grade 1 or Mild	Mild synovial hypertrophy without bulging over the line linking the tops of the bones Minimal joint effusion
Grade 2 or Moderate	Moderate synovial hypertrophy bulging over the line linking the tops of the bones but not extending to the diaphysis Minimal joint effusion
Grade 3 or Severe	Severe synovial hypertrophy bulging over the line with extension to at least one diaphysis Significant joint effusion

added together. These scores are presented in Table 3 for SH and Table 4 for PD.

Besides these semi-quantitative scores, a binary score (0 for the absence of synovitis and 1 for presence of synovitis) was used in one study [16].

Individual patient scores

The number of joints evaluated varied from six [14] to forty-four [12,19]. The scores including only six joints assessed those in the dominant hand. The wrist was included in all scores, with either all metacarpo-phalangeal joints (MCP) [14] or second to fifth MCP joints [9,10]. Certain authors assessed the joints of the feet as well as those of the hands [11,12,19,20]. Large joints, such as the shoulders, elbows, knees and ankles, were evaluated in two articles [12,19]. The sterno-clavicular and acromio-clavicular joints and hip joints were each included in one study [12,19]. The different scores are summarized in Table 5.

Table 4 Scoring of PD synovitis.

Grade 0	No PD signal
Grade 1	3 isolated spots or 2 confluent spots or 1 confluent spot and 2 isolated spots of signal
Grade 2	Vessel signals in < 50% of the areas of the synovium
Grade 3	Vessel signals in > 50% of the area of the synovium

Ultrasound results and findings

Detection of infra-clinical synovitis

In all the articles reviewed, there were significantly more synovites detected in B-mode or PD than the number of clinically swollen joints, although the frequency varied. Indeed, B-mode and PD synovitis were detected in 50.7% [20] to 95% of cases [19] and 14.7% [13] to 57.4% of cases, respectively [17]. Only three studies reported the exact number of clinically non swollen joints and the percentage of those with US synovitis among them [9,10,14]. This rate varied from 36 to 85% for US-SH and 15 to 50.5% for PD vascularization.

Predictive value for relapse

The predictive value of US for future relapse was studied in 3 out of 12 studies using the odds ratio (OR) [13,16,19]. In the study by Peluso et al. [16], the OR for relapse was 3.6 (95% CI: 1.4–9.0) in the presence of a Doppler signal and based on an evaluation of the wrist, second and third MCP joints and PIP joints on both hands. In the study of Foltz et al. [13], including the wrist, second to fifth MCP joints and PIP joints on both hands, a PD signal was predictive of relapse within a year with an OR of 6.5 (95% CI: 2.0–20). In the study by Sciré et al. [19] evaluating 44 joints, a Doppler signal predicted the risk of a future flare with an OR of 13 (95% CI: 1.6–104). The predictive value of B-mode for relapse was only studied in two articles and was not statistically significant [13,19].

Predictive value for structural progression

Two studies assessed the risk of structural progression in patients in clinical remission. In the first article by Brown et al. [10], including one hundred and two patients, eight joints (wrist and second to fifth MCP joints of the dominant hand) were assessed in each patient. B-mode SH was predictive of progressive structural deterioration with an OR of 2.31 (95% CI: 1.06–5.52) and the presence of a PD signal was also associated with articular damage within a year of follow-up with an OR of 4 (95% CI: 1.98–8.08). The second article by Foltz et al. [13] included 85 patients in whom fourteen joints were assessed on US. Both the presence of SH and a Doppler signal were predictive of structural progression with an OR of 1.92 (95% IC: 0.49–7.24) and of 1.4 (95% CI: 1.1–1.9), respectively.

Table 5 The different US scores adopted by the authors.

Authors reference	Number of joints assessed	Joints assessed
Saleem et al., [14]	6	Wrist 5 MCP Dominant hand
Brown et al., [9,10]	8	Wrist (4 joints) MCP 2-5 Dominant hand
Peluso et al., [16] Spinella et al., [17]	12	Wrists (medio- and radiocarpal) MCP 2-3 and PIP 2-3 Bilateral
Foltz et al., [13]	14	Wrists MCP 2-5 MTP 2-5 Bilateral
Saleem et al., [15]	18	Wrists MCP 2-5 PIP 2-5 Bilateral
Sakellariou et al., [23]	22	Wrists MCP PIP Bilateral
Wakefield et al., [20] Balsa et al., [11]	42	Shoulders, elbows, wrists, MCP, PIP, knees, ankles, MTP Bilataral
Sciré et al., [19]	44	Shoulders, sterno- and acromio-clavicular, elbows, wrists, MCP, PIP, knees, ankles, MTP Bilateral
Naredo et al., [12]	44	Wrists, MCP, PIP, elbows, shoulders, hips, knees, ankles, MTP Bilateral

MCP: metacarpo-phalangeal; PIP: proximal interphalangeal; MTP: metatarso-phalangeal.

Comparison of ultrasound abnormalities in the different remission scores

Three studies [11,12,16] compared US findings in relation to the different RA remission scores.

Balsa et al. [11] did not find any significant difference between modified ACR and DAS-28 criteria for the number of active joints, on B-mode or PD. Indeed, with PD, the median number of active joints was 2.07 ± 0.67 according to ACR criteria and 2.21 ± 0.79 according to DAS28 ($P = 0.49$). However, when using SDAI with a cutoff of < 3.3, the median number of joints with synovitis on PD was significantly lower than with ACR and DAS-28 criteria. If remission was defined as « absence of PD vascularized joints », the sensitivity and specificity of SDAI were 57.4 (95% CI: 44.2—69.7) and 74.4 (95% CI: 58.9—85.4) respectively. In the study by Naredo et al. [12], the median number of PD hypervascularized joints was significantly greater in patients in remission according to DAS-28 than in those in remission according to SDAI criteria. Peluso and al. [16] showed that there were fewer hypervascularized synovites using DAS remission criteria (< 1.6) than with ACR remission criteria (PD: 36.5% versus 83%).

Discussion

Twelve articles were evaluated in this review of the literature. They all assessed the role of US for detecting persistent disease activity, comparing the different activity scores or predicting future relapse or structural progression in RA in remission.

To define remission, most studies relied solely on the judgment of referring physicians [9—12]. However, when more objective criteria were applied, a great number of patients were no longer in remission. The most frequently used scores were those established by EULAR: DAS or DAS-28. According to these scores, remission is defined by a DAS < 1.6 or a DAS28 < 2.6 [21]. These scores have often been criticized because even when a patient fulfilled criteria for remission, the presence of synovitis may still be found on US [22]. Thus, all the studies that used DAS or DAS-28 remission criteria also found the presence of synovitis on US [13—17,19,20,23]. The SDAI and the Clinical Disease Activity Index (CDAI) [24] are simpler scores that have been shown to be highly effective, would be easier to use in daily clinical practice. These scores do not require special calculators. In fact, the SDAI is the numerical sum of five parameters:

tender joint count (TJC), swollen joint count (SJC) (based on a 28-joint assessment), patient global assessment (PGA), global physician assessment (GPA), and level of C-Protein Reactive (CRP) (Appendix 1). RA is considered to be in remission if this score is ≤ 3.3. CDAI is the numerical sum of four parameters: TJC + SJC + PGA + GPA. A score of ≤ 2.8 confirms the diagnosis of remission (Appendix 1). In two of the studies included in this review in which the SDAI score was used to define remission, fewer B-mode synovitis were detected on US [11,12]. The most recent criteria for remission are ACR/EULAR 2011. Remission is confirmed when the patient fulfills all of the following criteria at any time of the disease: TJC ≤ 1, SJC ≤ 1, CRP ≤ 1 mg/dL and PGA ≤ 1 (scale from 0—10) [25]. This score was only used in one study of Sakellariou [23] to assess remission.

A semi-quantitative score was used in B-mode and PD to each joint in all the studies reviewed. The score used was very similar to Szkudlarek's, which is the most widely accepted because of its simplicity and reproducibility. Other semi-quantitative scores are available such as Scheel's [26] in which B-mode SH is evaluated by measuring the height of the perpendicular line joining the diaphyseal cortex to the upper limit of the synovial surface, with a limit of 0.6 mm to distinguish normal from pathological effusion [26]. This quantitative assessment of synovitis might be more effective in diagnosing RA remission. Moreover, precise quantification of the Doppler signal can be obtained by counting the number of colored pixels on the synovial surface [27]. None of the studies evaluated used this method.

The scores used in the articles in this study included an evaluation between 6 and 44 joints. The wrist and MCP joints of the dominant hand were included in all scores. Exploration of large joints and the feet was rare. Naredo et al. [12] compared several US scores and showed that the score including the bilateral assessment of the wrists, second to fifth MCP joints, ankles and MTP joints seemed to have the strongest correlation with the score including 44 joints. In a review of the literature by Ten Cate and al. [28], a minimal score including the wrists, MCP and MTP joints was necessary to evaluate active RA. However, for RA in remission, assessment of the wrist and the MCP joints of the dominant hand was enough. Assessing only 6 joints presents a risk of ignoring other active joints, while evaluating 44 joints would be too time-consuming for daily clinical practice. A standardized US score that must be validated by expert medical societies is therefore essential. This is the goal of the Targeted Ultrasound Initiative (TUI), a group of rheumatologists and ultrasound specialists whose purpose is to establish new remission criteria that include US [29]. In all articles included in our review, whatever the remission criteria used and whether they were subjective or objective, persistent synovitis, even vascularized, were detected on US. This could be because a patient could fulfill remission criteria based on composite scores of RA activity (ACR, DAS, DAS28, SDAI), but still have a clinically swollen joint. However, Brown et al. and Saleem et al. [9,10,14] selected patients with no clinically swollen joints and, even in these cases, infra-clinical vascularized synovitis were detected on PD in 15 to 50% of the cases. The detection of infra-clinical synovitis in patients in remission could be very important for the prognostic of RA. Indeed, persistent infra-clinical synovitis has been shown to be predictive of a future flare and progressive structural deterioration [10,13,16]. The estimated risk of joint deterioration at 3 to 5 years was between 19 and 54% in patients in remission [30]. Whatever the remission criteria used, the frequency of synovitis varied considerably in the studies in this review from 50 to 95% with B-mode US, and 15 to 60% for PD. These differences are probably due to the different methodologies in these studies. First, the number of patients in remission who were included differed from a study to another (from 10 to 166 patients). Remission criteria also differed and in some articles, it was only based on the physician's judgment therefore including patients with active PA and creating a bias in US results. Finally, these differences could mainly be due to the number of joints evaluated (from 6 to 44).

In this review of the literature, only three authors compared US results among the different RA remission scores. There was no significant difference in the number of synovites based on B-mode or PD when a patient was in remission using ACR or DAS criteria. On the other hand, fewer synovites were detected on US in patients with RA in remission based on the SDAI score with a limit of ≤ 3.3, ($P = 0.006$) than with the DAS28. Thus, the SDAI score seems to have the strongest correlation with remission. Nevertheless, despite the use of these scores, infra-clinical synovitis can still be present [31]. Thus, US seems to be the only reliable technique to define remission.

Conclusion

The main goal in the treatment of RA is to achieve remission and to prevent structural damage, which is a major source of future disability. Several scores are available to define remission. According to this review of the literature on RA in remission and despite the heterogeneity of articles included, US synovitis was present in patients in remission whatever the score used. US activity was found to be at least 36% with B-mode and 15% with PD depending on the study. Moreover, persistent synovitis was predictive of possible relapse and joint deterioration. Ideally all joints should be evaluated to assess RA activity. However, in daily clinical practice, this would be tedious and time-consuming. To date, there is no validated score that precisely defines the joints to be explored. However, a good correlation has been found between evaluation of the wrist and MCP joints of the dominant hand and RA activity on remission. The same percentage of cases of infra-clinical synovitis was found in patients who were considered to be in remission on ACR criteria and the DAS or DAS28 scores, while fewer infra-clinical synovites were detected in those evaluated by the SDAI score, which therefore has a stronger correlation with remission. Finally, the confirmation of remission by US seems necessary to determine the therapeutic strategy, avoid relapse and especially future structural progression. While waiting for new criteria of RA in remission, US should be performed more frequently in daily practice and repeated if necessary.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix 1. Tables A—C DAS 28: DAS 28 is a composite score of RA activity developed by EULAR. Twenty-eight specific joints are assessed: ten metacarpo-phalangeal joints, eight proximal interphalangeal joints of the hands, two interphalangeal joints of the thumbs, two wrists, two elbows, twho shoulders and two knees. The score includes TJC and SJC on palpation, the VS and PGA results. It is calculated using the following formula: DAS 28 = $[0{,}56 \times \sqrt{(TJC)}] \pm [0{,}28 \times \sqrt{(SJC)}] \pm [0{,}7 \times Ln(VS)] \pm [0{,}014 \times (PGA)]$. The level of RA activity according to this score is summarized in Table A.

Table A Different levels of RA activity according to DAS 28.

DAS 28 value	≥ 5.1	$3.2 \leq$ DAS 28 ≤ 5.1	$2.6 \leq$ DAS 28 ≤ 3.2	≤ 2.6
Level of activity	High	Moderate	Low	Remission

Clinical Disease Activity Index (CDAI): CDAI is the numerical sum of four parameters: TJC + SJC (28 joints assessed) + PGA + PGA. The different levels of RA activity according to CDAI are summarized in Table B.

Table B Different levels of RA activity according to CDAI.

CDAI value	≥ 20	$10 \leq$ CDAI ≤ 20	≤ 10	≤ 2.8
Level of activity	High	Moderate	Low	Remission

Simple Disease Activity Index (SDAI): is the numerical sum of five parameters: TJC + SJC (28 joints assessed) + PGA + GPA + CRP. The different levels of RA activity according to SDAI are summarized in Table C.

Table C Different levels of RA activity according to SDAI.

SDAI value	≥ 26	$11 \leq$ SDAI ≤ 26	≤ 11	≤ 3.3
Level of activity	High	Moderate	Low	Remission

New ACR/EULAR criteria proposed in 2011: are particularly used in clincal trials. Remission is defined either by SDAI ≤ 3.3 or the following Boolean criteria: TJC ≤ 1, SJC ≤ 1, CRP ≤ 1 mg/L, et PGA ≤ 10.

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